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CYCLIZATIONS INVOLVING INTERMEDIATES OBTAINED BY SELECTIVE LITH--ETC(U)
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LEVEL II

CYCLIZATIONS INVOLVING INTERMEDIATES OBTAINED BY SELECTIVE LITHIATIONS

Final Report

by

Charles K. Bradsher

October 15, 1979

Army Research Office

Grant DAAG29 77G 0170

at

Department of Chemistry

Duke University

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19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

reagents, organolithium, functionalized; lithiation, selective; cyclizations, base-catalyzed; temperature, low, organic reactions at.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The discovery by Parham, et al. that the halogen-metal exchange reaction at low temperature can be used to generate organolithium reagents bearing electrophilic groups elsewhere in the molecule has been of importance in the development of novel cyclization reactions. If the anionic and electrophilic centers of the functionalized organolithium reagent thus generated are suitably arranged, an external electrophile may react to generate a new anion capable of (over)

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FOREWORD

The sudden and untimely death of Professor W. E. Parham on May 21, 1976, left an excellent group of four young graduate students each of whom was determined, if possible, to continue and expand the field of "Parham Chemistry" - the synthesis and elaboration of aryllithium reagents bearing functional groups. Since Dr. Parham's grant DAHCO4 74 GO128 expired April 30, 1977, we sought research support for the continuation project. The Army Research Office awarded Duke University the sum of $15,000 (over a two-year period) which was agreed to represent participation by ARO with Duke University in the support of the proposed research. The work described here was carried out by three of the four Parham students, David W. Boykin, David A. Hunt and David C. Reames, each of whom has now completed the requirements for the PhD. degree.

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(Publications acknowledging support of Grant No. DAAG29 77 G0170)

1. W. E. Parham, C. K. Bradsher and D. A. Hunt, "Reaction of Aryllithium Reagents with Nitriles. Synthesis of 1-Substituted 3,4-Dihydroisoquinolines," J. Org. Chem. **43**, 1606 (1978).

2. C. K. Bradsher and D. C. Reames, "A New Anionic Cyclization of the Parham Type Selective Ring Opening of Epoxides," J. Org. Chem. **43**, 3800 (1978).

3. C. K. Bradsher and David A. Hunt, "An Efficient Synthesis of 4,5-D-methoxycyclobutene *via* the Parham Cyclialkylation Reaction," Organic Preparations and Procedures, Int., **10**, 267 (1978).

4. David W. Boykin and W. E. Parham, "Reactions of Lithio Derivatives of Carboxylic Acids 2. Alkylations and Cyclizations of Substituted Acrylic Acids," J. Org. Chem., **44**, 424 (1979).

BODY OF REPORT

Halogen-metal exchange has long been known to be a useful method for preparation of organolithium compounds.[1] However, the reaction was at first limited to aryl bromides (or iodides) that contained no electrophilic functional groups; those groups precluded exchange, for they reacted with the exchange agent or with the generated aryllithium reagent. Parham and associates[2-4] found that this limitation could be removed if exchange was carried out at -100°C. At that temperature, many electrophilic groups (e.g., COOH, COOR, CN, CH_2Cl) were found to be passive toward attack by butyllithium while exchange of the aryl bromide remained facile. Thus, the low temperature exchange reaction provided a route to functionalized organolithium reagents.

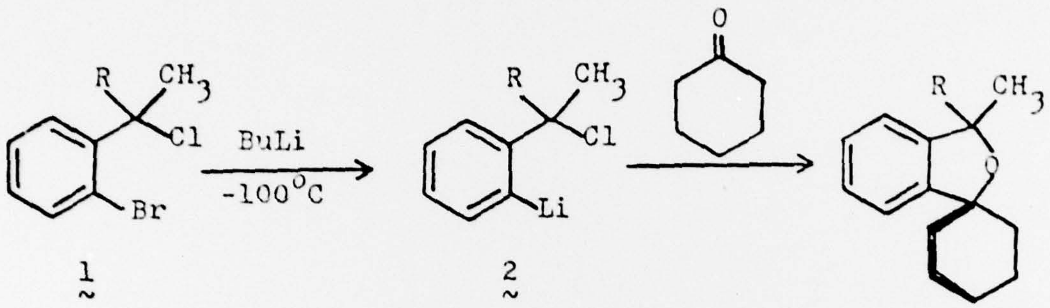
To demonstrate the synthetic utility of low temperature exchange, a variety of aryllithium reagents containing electrophilic groups were prepared by exchange at -100°C. These novel reagents were employed in two different synthetic sequences. In the first, the functionalized organolithium reagent was allowed to react with an added electrophile. Several exchange substrates were investigated in reactions of this type:

REACTIONS WITH EXTERNAL ELECTROPHILES

1. Benzylic Halides

α-Methyl-o-bromobenzyl chloride (**1a**, R = H) and α,α-dimethyl-o-bromobenzyl chloride (**1b**, R = CH_3) were both found to undergo selective exchange to the o-lithio derivatives (**2a** and

2b) when treated with butyllithium at -100°C. These reagents (**2**) reacted with cyclohexanone, an added electrophile, and cyclized to afford phthalans **3a** and **3b**.

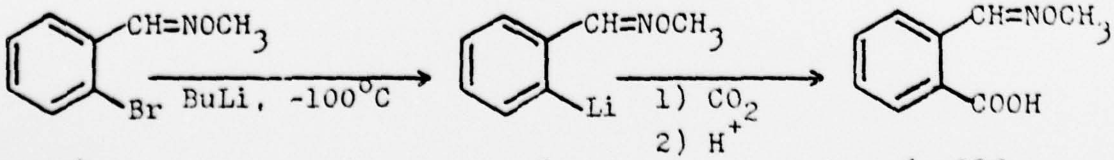


1 **2**

3a (R = H); 65%
3b (R = CH_3); 25%

2. *O*-Methyl Oximes of Aromatic Aldehydes

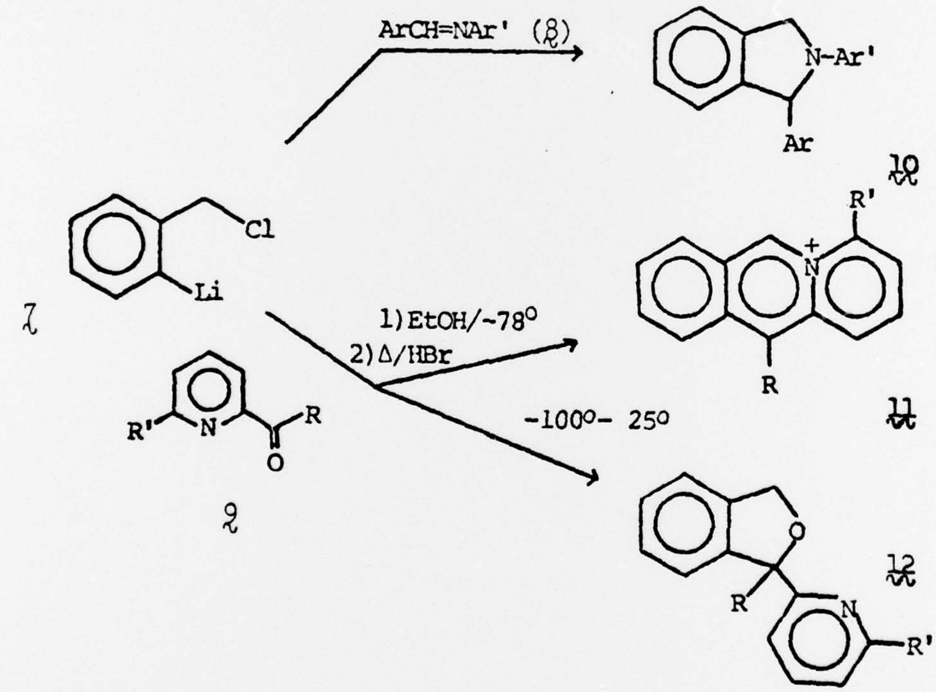
The aldehyde carbonyl remains reactive toward butyllithium even at -100°C and therefore must be protected during exchange. The *O*-methyl oxime of *o*-bromobenzaldehyde (**4**) was prepared and subjected to exchange; the organolithium reagent **5** was generated and could be trapped as acid **6** by carbonation. Surprisingly, when *o*-bromobenzaldehyde oxime was subjected to lithiation with two equivalents of butyllithium, exchange preceded abstraction of the weakly acidic oxime proton. An apparent rapid proton transfer then quenched the aryllithium reagent. Thus, the oxime itself was found to be unsatisfactory as an aldehyde protecting group during exchange.



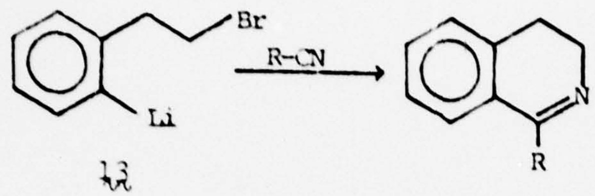
4 **5** **6**; 88%

3. Reaction of o-Lithiophenylalkyl Halides with External Electrophiles.

Reaction of o-lithiobenzyl chloride (7), prepared from the reaction of the corresponding bromide with n-butyllithium at -100°,[4] with Schiff bases (8) and pyridine-2-carbonyl derivatives (9) proved to be of value in the preparation of 1,2-diarylisoindolines (10). acridizinium salts (11), and dihydroisobenzofurans (6). It was found that whether 5 or 6 was prepared from the reaction of 8 with the pyridine-2-carbonyl derivatives (9) was highly temperature dependent.



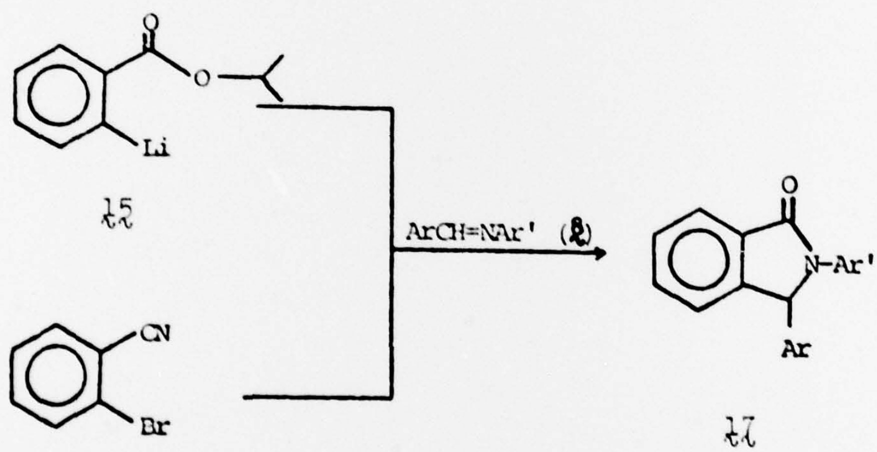
Reaction of o-lithio-β-phenylethyl bromide (13) (prepared from the corresponding bromide)[4] with nitriles proved to be a facile method for the preparation of 1-substituted-3,4-dihydroiso-quinolines (14).[5]



13 14

4. Reaction of Isopropyl-o-Lithiobenzoate and o-Lithiobenzonitrile with Schiff Bases.

Reaction of isopropyl-o-lithiobenzoate (15) and o-bromobenzonitrile (16) (prepared by the reaction of the corresponding bromides with n-butyllithium at -100°)[6,7] with Schiff bases (8) proved to be an entry into the 2,3-diaryl phthalimidine system (17).

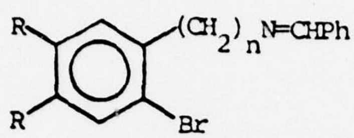


15 16 17

5. Studies of Bromine-Lithium Exchange with o-Bromoaryl Schiff Bases.

Reaction of n-butyllithium with Schiff bases of the type 18a-c gave varying results. In the case of 18a, addition to the azomethine linkage occurred in preference to exchance

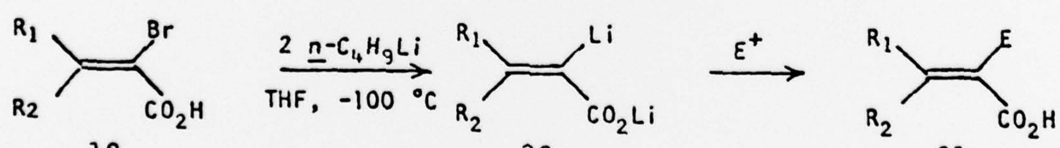
at -100°. In the case of 18b, a limited amount of exchange product could be detected at -100°.



18a, n=0
b, n=1
c, n=2

6. Derivatives of Acrylic Acid

The reactivity of derivatives of 2-bromoacrylic acid was investigated in detail. The reaction of 19a with two molar equivalents of n-butyllithium in tetrahydrofuran at -100°C afforded polymeric material. Compound 19b was found to undergo dehydrobromination to phenylpropynoic acid, even at -140°C. Bromine-lithium exchange was rapid and complete for 19c and 19d, which afforded the lithiovinyl derivatives 20a and 20b, respectively.



19
a, $R_1 = R_2 = H$
b, $R_1 = Ph$ $R_2 = H$
c, $R_1 = R_2 = CH_3$
d, $R_1 = R_2 = Ph$

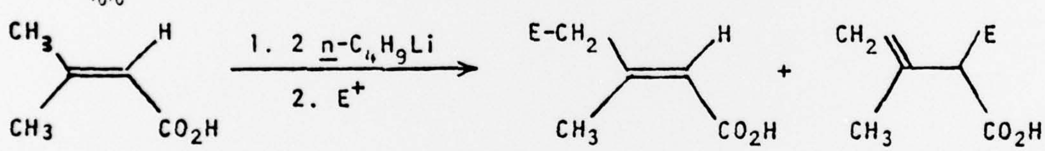
20
a, $R_1 = R_2 = CH_3$
b, $R_1 = R_2 = Ph$

21
a, $R_1 = R_2 = CH_3$
b, $R_1 = R_2 = Ph$

These reagents were used to alkylate a variety of electrophiles to afford 2-substituted acids of types 21a and 21b.[8]

Electrophile	Product		Isolated Yield, %
CH_3CH_2I	21a, E =	CH_2CH_3	79
CH_3OD	"	D	98
$C_6H_5SSC_6H_5$	"	SC_6H_5	61
C_6H_5NCO	"	$CONHC_6H_5$	58
CH_3I	21b, E =	CH_3	73
Cyclohexanone	"	$C(OH)(CH_2)_5$	62
$C_6H_5SSC_6H_5$	"	SC_6H_5	68
$C_6H_5CH_2SSCH_2C_6H_5$	"	$SCH_2C_6H_5$	61

The reaction of 3-methyl-2-butenoic acid (22) with n or tert-butyllithium was found to produce a lithio derivative which underwent α-and γ-alkylation and/or double bond isomerization, a result also obtained by the use of lithium diisopropyl amide with 22.[9]

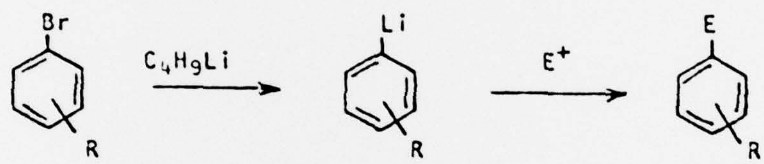


22 23 24

7. Bromoaryl Compounds

A comparison of the reactivities of the isomeric lithium lithio benzoates and synthetically related organolithium compounds (26, 29, and 32) was made by using the alkylation of chlorosilanes (e. g., $(CH_3)_3SiCl$) and disulfides (e. g., CH_3SSCH_3) as model reactions. These were prepared by low temperature lithiation of the corresponding bromoaryl compounds (25, 28, 31).[3,6,7] The

The lithioaryl carboxylates 29b and 32b gave variable yields of alkylation products and were generally inferior to the isomer 26b. The alkylation of 29d and 32d followed by acid-catalyzed hydrolysis of the tert-butyl group provided an alternative route to acids 30a and 33a (E = $(CH_3)_3Si$). The lithio derivatives of the isomeric nitriles (16e, 29e, and 32e) were all efficiently alkylated. A variety of o-substituted benzoic acids (27a) and benzonitriles (27e) were prepared: 27a, E = $Si(CH_3)_3$, $Si(CH_3)_2Ph$, SCH_3, SPh, SCH_2Ph, SePh, PPh_2, $P^+Ph_2CH_3$ I^-; 27e, E = $Si(CH_3)_3$, $Si(CH_3)_2Ph$, SCH_3, SPh, $S(CH_3)_2^+$ BF_4^-, PPh_2, $P(O)Ph_2$, $P(S)Ph_2$, $P^+Ph_2CH_3$ I^-. Other isomers and esters prepared included: 27c, E = SCH_3, $S(CH_3)_2^+$ BF_4^-; 27d, E = SCH_3, $Si(CH_3)_3$, 30e, E = SCH_3; 30d, E = $Si(CH_3)_3$; 33d, E = $Si(CH_3)_3$, 33e, E = SCH_3.



ortho:	25	26	27
meta:	28	29	30
para:	31	32	33

a, R = CO_2H

b, R = CO_2Li

c, R = $CO_2CH(CH_3)_2$

d, R = $CO_2C(CH_3)_3$

e, R = $C{\equiv}N$

8. Saturated Bromo Acids

11-Bromoundecanoic acid (**34**) was converted to the trilithio derivative **35** which afforded 11-(phenylthio)undecanoic acid (**36**) in 52-53% yield.

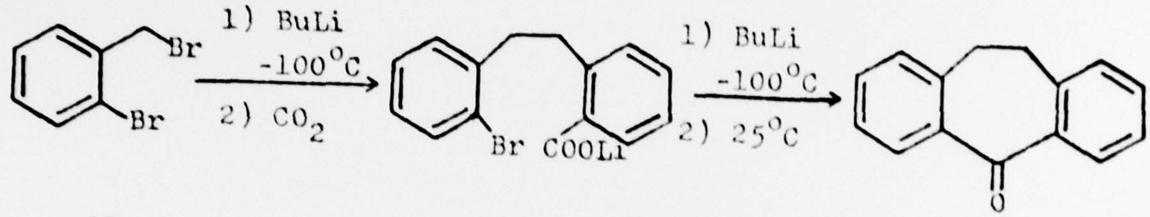
$$\underset{\mathbf{34}}{Br(CH_2)_{10}CO_2H} \longrightarrow \underset{\mathbf{35}}{Li(CH_2)_9CH{=}CO_2Li_2} \longrightarrow \underset{\mathbf{36}}{PhS(CH_2)_{10}CO_2H}$$

REACTIONS WITH INTERNAL ELECTROPHILES

In the case of other functionalized organolithium reagents generated by exchange, the electrophilic group was positioned such that it could act as an internal electrophile and afford a cyclic product. This synthetic sequence, the Parham cyclization, was further developed as an alternative to traditional ring closures in investigations on several systems:

1. Acids

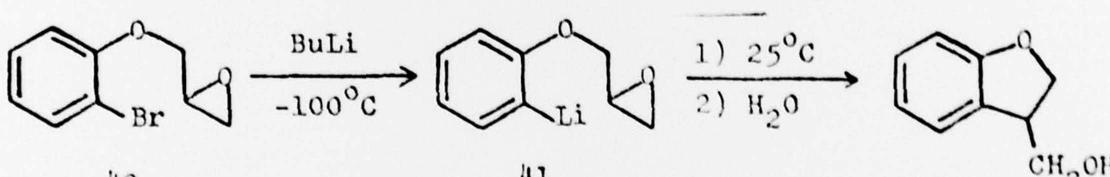
Parham, Jones, and Sayed[3] have reported the use of the lithium salt of a carboxylic acid as an internal electrophile in a synthesis of 1-indanone. This cyclization was extended to the preparation of seven-membered ring ketones and heterocyclic ketones. Of particular interest was a novel synthesis of dibenzosuberone (**39**). *o*-Bromobenzyl bromide (**37**) was converted to 2-bromo-2'-lithiobibenzyl;[4] carbonation gave salt **38**. Exchange and cyclization gave dibenzosuberone (**39**; 56% from **37**) in an efficient, "one-pot" procedure.



37 38 39; 56%

2. Epoxides

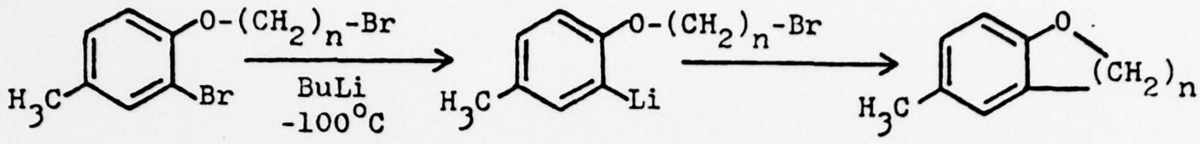
The epoxide ring was found to be passive toward attack by butyllithium at -100°C; thus, it was possible to generate aryllithium reagents of type 41. These reagents were particularly interesting, for rings of two different sizes might be formed in the Parham cyclization. However, for a number of examples,[10] the only cyclic product was the 2,3-dihydro-3-benzofuranmethanol (42). No six-membered ring product was detected even in cases where the epoxide carbon nearer the anionic center was fully substituted.



40 41 42; 64%

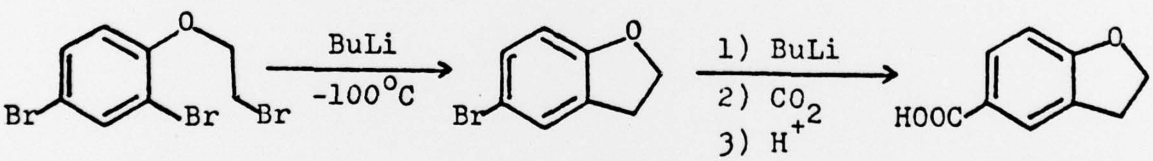
3. Phenoxyalkyl Halides

The Parham cyclialkylation, previously reported only in carbocyclic systems,[4] was extended to the preparation of substituted oxygen heterocycles. Substituted o-bromophenoxyalkyl bromides such as 43 (n = 2-4) were found to undergo rapid exchange to intermediates 44 (n = 2-4). Cyclization of these reagents gave good yields of products (45).



43 44 45 (n = 2-4); 69-73%

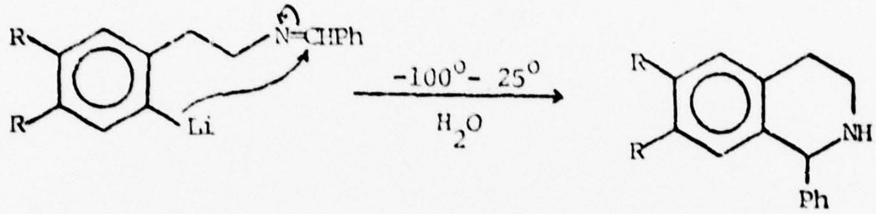
The phenoxyalkyl bromides were also studied as substrates for double lithiations (i.e., two successive selective exchange reactions on one aryl nucleus). For example, compound 46 was found to undergo selective exchange and cyclization to heterocycle 47. Without isolation of 47, a second exchange and a reaction with an added electrophile (CO_2) could be carried out, giving acid 48. Additional examples of double lithiations demonstrated the versatility this technique imparts to the exchange process.



46 47 48; 61%

4. <u>Schiff Bases</u>

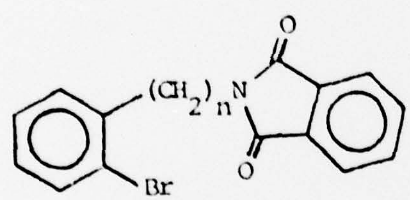
The best results were observed for Schiff bases of the type 49c. Bromine-lithium exchange occurred readily at -100°, and upon warming the lithio derivative 49 to room temperature, 1-substituted-1,2,3,4-tetrahydroisoquinolines (50) were obtained *via* intramolecular attack of the "anion" upon the azomethine linkage.



49 50

5. Studies of Bromine-Lithium Exchange in Systems Containing a N-C=O Linkage.

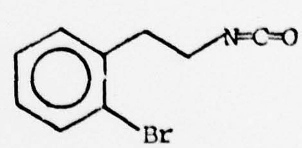
Attempted bromine-lithium exchange by the reaction of n-butyllithium with bromophthalimides (51a-c) and o-bromo-β-phenylethyl isocyanate (52) at -100° failed in all cases tested, the major product obtained in each case derived from the addition of nbutyllithium to the N-C=O linkage.



51a n=0

b, n=1

c, n=2



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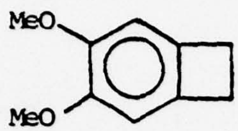
6. Bromine-Lithium Exchange Studies of Bromo-β-Arylethyl Bromides.

Bromine-lithium exchange in systems analogous to o-lithio-β-phenylethyl bromide (13) proved to be a valuable technique for the large scale preparation of arylcyclobutenes 53 and 54.[9]



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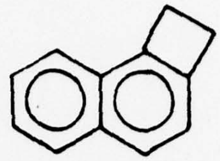

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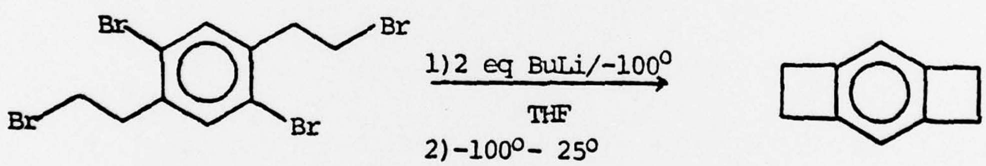
Additionally, bromine-lithium exchange studies with the arylbromo compound 55 proved to be a new method for the large scale preparation of 1,3,4,5-benzodicyclobutene (56); however, if substituents are placed at the 3- and 6- positions (as in 57), a single exchange occurs, even when treated with two equivalents of n-butyllithium. This phenomenon is presumably due to anion formation in order to relieve steric strain.



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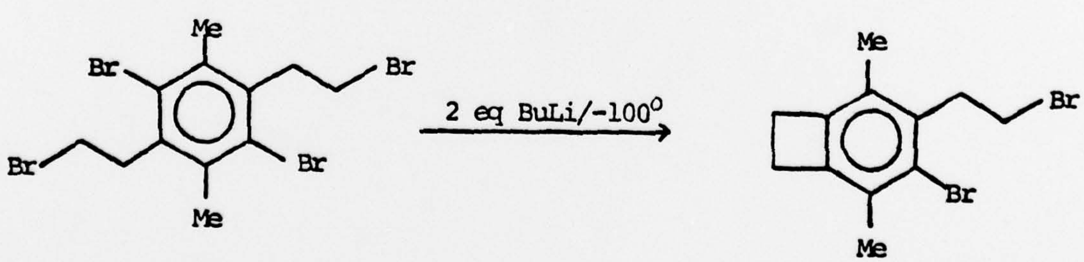

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bromoethyl, cyano, carboxylate, carboalkoxy as well as beta carboxyethyl anion and beta carboxamidoethyl groups.

Functionalized phenyllithium reagents have great synthetic utility. Reaction with electrophiles, such a methyl iodide, bromine, benzaphenone, cyclohexonone, phthalic anhydride, benzoate esters, diphenyl disulfide or ethylene oxide replaces the aryl lithium atom resulting in a benzene ring with two functional groups.

Usually, allowing the functionalized aryllithium to warm up results in an interaction between the lithium atom and the functional group. A useful example of such an interaction is the self condensation of lithium ortho-lithio benzoates to yield ortho-benzoylbenzoic acid.

A phenyllithium reagent having a functional substituent in the ortho position are frequently useful intermediates for cyclization.